Mortality of HIV-1-infected patients in the first year of antiretroviral therapy: comparison between low-income and high-income countries

The Antiretroviral Therapy in Lower Income Countries (ART-LINC) Collaboration and ART Cohort Collaboration (ART-CC) groups

Summary

Background Highly active antiretroviral therapy (HAART) is being scaled up in developing countries. We compared baseline characteristics and outcomes during the first year of HAART between HIV-1-infected patients in low-income and high-income settings.

Methods 18 HAART programmes in Africa, Asia, and South America (low-income settings) and 12 HIV cohort studies from Europe and North America (high-income settings) provided data for 4810 and 22 217, respectively, treatment-naïve adult patients starting HAART. All patients from high-income settings and 2725 (57%) patients from low-income settings were actively followed-up and included in survival analyses.

Findings Compared with high-income countries, patients starting HAART in low-income settings had lower CD4 cell counts (median 108 cells per μL *vs* 234 cells per μL), were more likely to be female (51% *vs* 25%), and more likely to start treatment with a non-nucleoside reverse transcriptase inhibitor (NNRTI) (70% *vs* 23%). At 6 months, the median number of CD4 cells gained (106 cells per μL *vs* 103 cells per μL) and the percentage of patients reaching HIV-1 RNA levels lower than 500 copies/mL (76% *vs* 77%) were similar. Mortality was higher in low-income settings (124 deaths during 2236 person-years of follow-up) than in high-income settings (414 deaths during 20 532 person-years). The adjusted hazard ratio (HR) of mortality comparing low-income with high-income settings fell from 4·3 (95% CI 1·6–11·8) during the first month to 1·5 (0·7–3·0) during months 7–12. The provision of treatment free of charge in low-income settings was associated with lower mortality (adjusted HR 0·23; 95% CI 0·08–0·61).

Interpretation Patients starting HAART in resource-poor settings have increased mortality rates in the first months on therapy, compared with those in developed countries. Timely diagnosis and assessment of treatment eligibility, coupled with free provision of HAART, might reduce this excess mortality.

Lancet 2006; 367: 817–24

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Introduction

The increasingly widespread use of highly active antiretroviral therapy (HAART) since 1996 has substantially improved the prognosis of HIV-infected patients who have access to these drugs.[1–4] In resource-poor settings in Africa, Asia, and South America, where 90% of people with HIV/AIDS live, access to HAART is limited. With falling prices of proprietary drugs, the increasing availability of generic formulations and the launch of initiatives by international agencies, including the World Health Organization's (WHO's) "3 by 5" programme (to get 3 million HIV patients on antiretrovirals by 2005), the Global Fund to fight AIDS, Tuberculosis and Malaria, and the US President's Emergency Plan for AIDS Relief (PEPFAR), this situation is changing. The WHO estimates that as of June, 2005, about 1 million people were receiving HAART, although this number still only represents 15% of the estimated 6·5 million people in urgent need of antiretroviral therapy in low-income and middle-income countries.[5]

Several factors could limit the effectiveness of HAART in resource-poor settings. Interruptions in supply at the programme level or patients' limited financial resources might compromise adherence and treatment efficacy. The high prevalence of co-infections, notably with tuberculosis and other bacterial diseases might also affect prognosis.[6–8] Here we report on the Antiretroviral Therapy in Lower Income Countries (ART-LINC) Collaboration, a network of treatment programmes in Africa, Asia, and South America.[9] Our objective was to compare early mortality and immunological and virological response in patients starting HAART in these settings with outcomes in patients participating in a similar collaboration of cohort studies in high-income countries, the ART Cohort Collaboration (ART-CC).[1]

Methods

Participants

Treatment programmes in low-income countries were identified by searching published scientific reports, including abstracts from recent conferences, and by consulting with colleagues. Site assessments were done with a standardised questionnaire. Programmes that collected prospective data on patient characteristics and outcomes were eligible for inclusion in ART-LINC. 23 treatment programmes were approached, 19 agreed to participate, and 18 of these contributed data to this analysis.

Information obtained for patients included sociodemographic data, date of starting HAART, and,

where available, CD4 cell counts and HIV-1 RNA levels at baseline and during follow-up. Type of regimen was defined as protease inhibitor-based (one protease inhibitor and two nucleoside reverse transcriptase inhibitors [NRTIs], including ritonavir-boosted regimens), non-nucleoside reverse transcriptase inhibitors [NNRTI] based (one NNRTI and two NRTIs), or other combinations (including triple NRTI regimens and any other regimen containing a minimum of three drugs). Programme characteristics were also recorded, including the use of generic drugs, virological monitoring, costs to patients, tracing of patients who had been lost to follow-up, and other services, including voluntary counselling and testing, and tuberculosis clinics. We defined routine monitoring of virological response as at least one viral load measurement between 3 and 9 months after starting HAART, in at least 50% of patients.

The ART-CC is a collaboration of cohort studies and clinical databases from North America and Europe, established in 2001 to estimate prognosis in treatment-naive HIV-infected patients initiating HAART. Eligibility criteria and methods have been reported elsewhere.[1,10] We included all patients in each of the two collaborations who had not previously received antiretroviral therapy, were aged 16 years or older, with known date of starting HAART and a documented baseline CD4 count. The stage of disease was classified as either less advanced (CDC stage A/B, WHO stage I/II) or more advanced (CDC stage C, WHO stage III/IV). The selection of patients and extraction of data was done at the participating centres. Anonymous data were pooled and analysed centrally. At all sites, institutional review boards had approved the collection of data. We use the terms low-income and high-income settings for the treatment programmes participating in the ART-LINC and ART-CC collaborations, respectively.

Outcomes

The primary endpoint was mortality from all causes in the first year after starting HAART. Changes in CD4 cell counts in the first 6 months, and the proportion of patients with viral load less than 500 copies/mL at 6 months were secondary endpoints. Measurements closest to 6 months after starting HAART, within 3 to 9 months, were used in these analyses. We used an intent-to-continue treatment approach, and ignored changes to treatment, treatment interruptions and terminations. Time was measured from the start of HAART and ended at the earliest of: the date of death; the date of the last follow-up visit; or month 12 after starting HAART. A patient was judged to be lost to follow-up if the last visit was recorded during the first year after starting HAART and the patient had at least 1 year of additional potential follow-up until the closing date of the database. The closing date was defined for each cohort as the date of the most recent follow-up recorded in the database.

Statistical analysis

In ART-LINC, disease stage at the time of starting treatment was not available for all patients. Stage of disease is strongly associated with other variables—in

	Country	Free access to treatment	Use of generic drugs	Routine virological testing	Voluntary counselling and testing	Tuberculosis clinic on site	n (%)	Active follow-up	Proportion lost to follow-up
North Africa									
Morocco ART cohort	Morocco	Yes	No	Yes	No	Yes	300 (6%)	Yes	11 (4%)
Southern Africa									
Gaborone Independent	Botswana	No	No	Yes	Yes	No	209 (4%)	Yes	12 (6%)
Lighthouse	Malawi	No	Yes	No	Yes	No	1056 (22%)	No	325 (31%)
CTAC	South Africa	Yes	No	Yes	Yes	No	305 (6%)	Yes	46 (15%)
Khayelitsha	South Africa	Yes	Yes	Yes	Yes	Yes	278 (6%)	Yes	0%
OPERA	South Africa	Yes	No	Yes	Yes	No	53 (1%)	Yes	0%
East Africa									
Nsambya	Uganda	No	Yes	No	Yes	Yes	236 (5%)	Yes	104 (44%)
GATP Kampala	Uganda	No	Yes	Yes	No	No	74 (2%)	Yes	0%
Eldoret	Kenya	Yes	Yes	No	Yes	Yes	663 (14%)	Yes	91 (14%)
Central and west Africa									
Parvy	Cameroon	Yes	Yes	Yes	Yes	Yes	115 (2%)	Yes	51 (44%)
COTRAME	Côte d'Ivoire	Yes	No	No	Yes	Yes	131 (3%)	Yes	0%
Nigeria HAART	Nigeria	No	Yes	No	Yes	Yes	102 (2%)	Yes	0%
ISAARV	Senegal	Yes	Yes	Yes	Yes	Yes	146 (3%)	Yes	16 (11%)
HIMS	Various	Yes	Yes	No	Yes	No	81 (2%)	Yes	0%
South America									
Rio de Janeiro HIV	Brazil	Yes	Yes	Yes	No	Yes	429 (9%)	No	35 (8%
SobrHIV	Brazil	Yes	Yes	Yes	Yes	Yes	496 (10%)	No	28 (6%)
Asia									
YRG Care	India	No	Yes	No	Yes	Yes	104 (2%)	No	8 (8%)
HIV-NAT	Thailand	Yes	Yes	No	No	No	32 (0·66%)	Yes	0%

Details of treatment programmes listed at end of report.

Table 1: **Characteristics of antiretroviral treatment programmes in ART-LINC**

particular, CD4 cell count. We therefore created multiple datasets in which disease stage was imputed on the basis of whether the patient died, which cohort they were in, CD4 count, age, sex, and type of HAART regimen. In these imputations, values of the missing data were randomly sampled from their predicted distributions.[11,12] Analyses were run on each of 20 datasets, including the imputed values, and the results combined with Rubin's rules.[12] We used random-effects Weibull regression models to estimate mortality hazard ratios accounting for heterogeneity between treatment programmes.[13,14] Models included both individual level (age, sex, baseline CD4 cell count, type of initial regimen, and stage of disease) and programme level characteristics (free of charge treatment, use of generic drugs, routine monitoring of virological response, tuberculosis clinic on site, and intensity of efforts to trace patients). We used a parametric bootstrap procedure with 300 bootstrap replications to derive confidence intervals for cumulative hazards at months 6 and 12. Finally, we compared mortality between low-income and high-income settings, adjusting for differences in age, sex, baseline CD4 cell count, type of initial regimen, and stage of disease. We used Stata software (version 9) for analyses. Results are presented as estimates of the probability of death, mortality rates, and hazard ratios (HRs) with 95% CIs.

Role of the funding source

The sponsors of the study had no role in study design; the collection, analysis, or interpretation of data; the writing of the report; or the decision to submit the paper for publication.

Results

The ART-LINC dataset has 6498 treatment-naïve patients with a known date of starting HAART and at least one follow-up; 4810 (74%) patients also had a CD4 count at baseline, and were thus included in the analysis. Compared with treatment-naive patients starting HAART without an immunological assessment, those with a documented baseline CD4 count were less likely to be male and more likely to be treated in publicly funded centres or programmes offering free care.[9] The characteristics of the programmes contributing data to the present analysis are shown in table 1. Eligibility criteria for initiating HAART were generally advanced immunodeficiency or clinical disease. Six programmes were publicly funded through government and the remaining were run by non-governmental organisations or private doctors. All programmes included CD4 cell count monitoring, with measurements planned every 4–6 months. Routine monitoring of virological response was done in 10 programmes. 14 treatment programmes actively followed-up patients with telephone calls (often to mobile phones), letters, or home visits. 12 clinics provided free access to treatment. Costs to patients in the remaining six clinics varied from $8–198 per month for drugs, $15–33·50 per CD4 count, and $30–100 per viral load measurement. The number of patients included in this analysis ranged from 32 to 1056 patients, the proportion lost to follow-up from 0% to 44%.

	Low-income settings (n=4810)		High-income settings (n=22217)	
	n (%)*	Deaths	n (%)*	Deaths
Age (years)				
16–29	1013 (21%)	33 (20%)	4125 (19%)	42 (10%)
30–39	2188 (45%)	80 (48%)	10421 (47%)	161 (39%)
40–49	1177 (24%)	36 (22%)	5043 (23%)	108 (26%)
⩾50	432 (9%)	16 (10%)	2628 (12%)	103 (25%)
Median (IQR)	36 (30–42)	..	36 (31–43)	..
Sex				
Female	2461 (51%)	86 (52%)	5486 (25%)	79 (19%)
Male	2349 (49%)	79 (48%)	16731 (75%)	335 (81%)
Baseline CD4 (cells/μL)				
<25	917 (19%)	66 (40%)	2081 (9%)	113 (27%)
25–49	557 (12%)	25 (15%)	1350 (6%)	58 (14%)
50–99	805 (17%)	30 (18%)	2181 (10%)	52 (13%)
100–199	1217 (25%)	30 (18%)	4038 (18%)	87 (21%)
200–349	940 (20%)	10 (6%)	6018 (27%)	66 (16%)
⩾350	374 (8%)	4 (3%)	6549 (30%)	38 (9%)
Median (IQR)	108 (37–210)	..	234 (98–380)	..
Clinical stage				
CDC stage A/B, WHO stage I/II	867 (18%)	13 (8%)	17142 (77%)	154 (37%)
CDC stage C, WHO stage III/IV	1733 (36%)	97 (59%)	5075 (23%)	260 (63%)
Unknown	2210 (46%)	55 (33%)	0 (0%)	..
Initial antiretroviral regimen				
NNRTI-based	3391 (70%)	120 (73%)	5125 (23%)	71 (17%)
Protease inhibitor-based	900 (19%)	30 (18%)	13783 (62%)	276 (67%)
Unknown or other combination	519 (11%)	15 (9%)	3309 (15%)	67 (16%)

*Data are n (%) unless otherwise indicated.

Table 2: **Baseline characteristics and mortality in first year of HAART treatment in low-income and high-income countries**

The characteristics of the 12 cohorts from high-income countries (ART-CC) have been described elsewhere.[1] The 2004 database includes information on 22 217 patients who were followed-up in nine cohorts from Western Europe, two from Canada, and one from the USA. The cohorts and number of patients included in ART-CC are: French Hospital Database on HIV[15] (n=9167), AIDS Therapy Evaluation project Netherlands[16] (2720), Italian Cohort of Antiretroviral-Naïve Patients[17] (2203), Swiss HIV Cohort Study[18] (2141), EuroSIDA[19] (1144), Frankfurt cohort[20] (1031), Collaborations in HIV Outcomes Research US (CHORUS)[21] (981), Köln/Bonn Cohort[22] (759), Aquitaine Cohort[23] (649), Royal Free Hospital Cohort[24] (647), British Columbia Centre for Excellence in HIV/AIDS[2] (507), and South Alberta Clinic[25] (268). All cohorts follow-up patients actively with telephone or postal reminders, or both. Recording of deaths in ART-CC can be assumed to be near complete: in two cohorts, deaths are routinely ascertained from the national mortality register, and mortality rates in these two cohorts are similar to that in the others.

Patients from low-income countries were more likely to be female and more likely to start HAART with a NNRTI-based regimen (table 2). The proportion of participants who were women ranged from 29% in India

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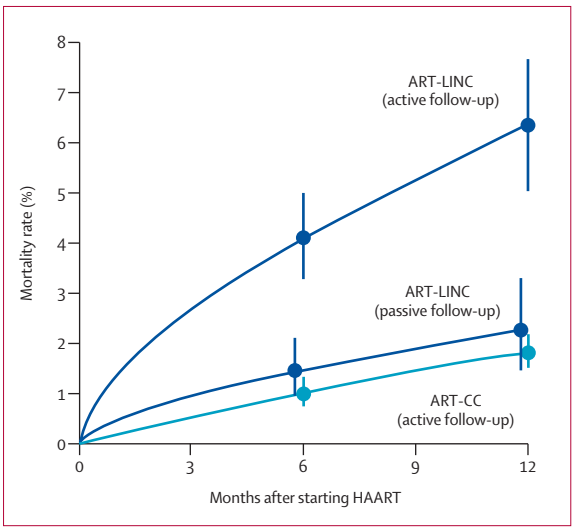

Figure 1: **Estimated cumulative probability of death in HAART programmes in low-income and high-income countries**
Vertical bars are 95% CIs.

to 79% at a site in South Africa; corresponding proportions in high-income countries ranged from 9% (CHORUS, USA) to 31% (Swiss HIV Cohort Study). In patients from low-income settings, the median CD4 cell count at the time of starting HAART was 108 cells per μL (IQR 37–210) compared with 234 cells per μL (98–380) in patients from Europe and North America. Information on clinical stage was available for 2660 (54%) patients from low-income settings and for all patients from high-income settings. The route of infection was recorded in few patients in low-income countries, but most are assumed to have been infected through heterosexual intercourse. Conversely, in high-income cohorts, sex between men was the most frequent risk factor (8777 patients, 40%), followed by heterosexual sex (7910, 36%) and intravenous drug use (3553, 16%).

	Hazard ratio (95% CI)	
	Low-income settings (n=2725)	High-income settings (n=22 217)
Age (years)		
16–29	1	1
30–39	1·12 (0·70–1·81)	1·16 (0·82–1·64)
40–49	1·09 (0·62–1·94)	1·47 (1·02–2·11)
⩾50	1·53 (0·74–3·18)	2·57 (1·78–3·71)
Sex		
Male	1	1
Female	0·84 (0·58–1·22)	0·85 (0·66–1·09)
Baseline CD4 (cells/μL)		
<25	1	1
25–49	0·77 (0·46–1·28)	0·83 (0·61–1·15)
50–99	0·54 (0·32–0·90)	0·55 (0·40–0·77)
100–199	0·37 (0·22–0·64)	0·67 (0·50–0·90)
200–349	0·14 (0·06–0·35)	0·44 (0·32–0·62)
⩾350	0·34 (0·12–1·01)	0·26 (0·17–0·39)
Clinical stage*		
CDC stage A/B, WHO stage I/II	1	1
CDC stage C, WHO stage III/IV	2·02 (1·02–4·02)	3·75 (2·96–4·74)
Initial regimen		
Two NRTIs+one NNRTI	1	1
Two NRTIs+one protease inhibitor	1·35 (0·76–2·40)	1·00 (0·77–1·31)
Unknown or other combination	1·13 (0·54–2·35)	1·17 (0·83–1·64)

*Imputed for only 649 patients from low-income settings.

Table 3: **Hazard ratios of progression to death in HAART programmes in low-income and high-income countries**

In low-income settings, 2725 (57%) patients were treated in programmes with active follow-up procedures and 3029 (63%) had free access to HAART. Webtables 1 and 2 compare the characteristics of patients treated in programmes with active and passive follow-up, and those in programmes free of charge and those that were not free. 727 (15%) and 1104 patients (5%) were lost to follow-up during the first year of therapy in low-income and high-income settings, respectively. In low-income settings, loss to follow-up was 12% (331 of 2725) in programmes with active follow-up and 19% (396 of 2085) in programmes with passive follow-up; loss to follow-up occurred after a median of 5·8 months (IQR 2·5–7·7) and 3·4 months (1·4–6·9), respectively. In treatment programmes with active follow–up, those lost to follow-up and those followed-up at 1 year had similar baseline CD4 cell counts (median 115 cells per μL and 123 cells per μL), whereas patients lost to follow-up in programmes with no active follow-up procedures had considerably lower CD4 cell counts than those followed-up (median 64 cells per μL and 123 cells per μL). Webtable 3 compares the characteristics of patients lost to follow-up with patients in active follow-up for both active and passive follow-up programmes.

After 6 months of treatment, CD4 and HIV-1 RNA measurements were available for 2789 (57%) and 2003 (48%) patients, respectively, in low-income settings, and in 19560 (88%) and 19164 (86%) in high-income settings. In low-income settings, patients with CD4 counts and viral load measurements at 6 months started HAART 1–2 years earlier, had higher CD4 cell counts at baseline, and were more likely to be treated in a programme providing free access to HAART than patients with no measurements. The median number of CD4 cells gained was 106 cells per μL (IQR 43–180) in low-income countries and 103 cells per μL (32–192) in high-income countries. 1527 (76%) in low-income settings and 14825 (77%) in high-income countries had HIV-1 RNA levels lower than 500 copies per mL at 6 months.

At 1 year, mortality was estimated at 6·4% (95% CI 5·1–7·7) in low-income programmes with active follow-up (based on 124 deaths and 2236 person-years of follow-up), 2·3% (1·5–3·2) in low-income programmes with passive follow-up (41 deaths and 1508 person-years follow-up), and 1·8% (1·5–2·2) in programmes from high-income countries (414 deaths and 20 532 person-years follow-up) (figure 1). Treatment programmes with passive follow-up were excluded from subsequent analyses.

Baseline CD4 cell count was strongly prognostic both in low-income and high-income settings: the lower the baseline CD4 cell count, the higher the mortality rate

(table 3). Older age and more advanced clinical stage were also associated with increased mortality. Among patients actively followed up, after imputation of missing information, an estimated 1608 patients (59·0%) had more advanced disease, whereas 504 patients (18·5%) had less advanced disease with a CD4 cell count above 200 cells per μL. There was little evidence for differences in progression rates between men and women or between patients starting HAART with different regimens.

In low-income settings, mortality was substantially higher in the first months after starting HAART than in later months. Mortality rates per 1000 person-years were 147 (95% CI 105–207) during month 1, 106 (71–160) in month 2, 51 (33–77) in months 3–4, 51 (33–79) in months 5–6, and 27 (19–40) in months 7–12. This trend was also noted in high-income settings, with mortality falling from 24 (21–27) during the first 6 months to 16 (14–19) during months 7–12. 97 (78%) of 124 deaths in low-income settings and 255 (62%) of 414 deaths in high-income countries happened in the first 6 months. Figure 2 shows crude and adjusted hazard ratios, comparing mortality in low-income countries to that in high-income settings, by time period after starting HAART. Adjusted hazard ratios fell from 4·31 (95% CI 1·57–11·81) during the first month on HAART to 1·48 (0·73–3·01) during the second half of the first year on HAART.

We assessed whether characteristics of treatment programmes in low-income settings affected outcome (table 4). In multivariable analysis, free access to treatment (with no costs to patients) was associated with lower mortality, whereas higher mortality was seen in programmes that included a tuberculosis clinic. There was little evidence for an association between mortality during the first year and the use of generic drugs or the routine monitoring of virological response.

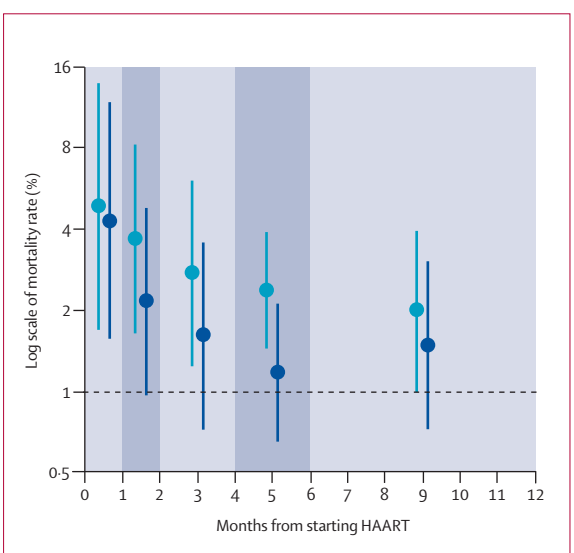

Figure 2: **Comparison of mortality in the months after starting HAART in low-income and high-income settings**
Shaded areas represent the periods for which hazard ratios were calculated. Vertical bars are 95% CIs. Light blue=unadjusted hazard ratios. Dark blue=hazard ratios adjuusted for all variables in table 3.

	Hazard ratio (95% CI)	
	Unadjusted	Adjusted
Free access to treatment		
No	1	1
Yes	0·45 (0·13–1·54)	0·25 (0·08–0·78)
Use of generic drugs		
No	1	1
Yes	1·78 (0·52–6·13)	1·40 (0·45–4·39)
Routine monitoring of virological response		
No	1	1
Yes	1·43 (0·42–4·90)	2·28 (0·76–6·79)
Tuberculosis clinic on site		
No	1	1
Yes	2·42 (0·71–8·28)	3·76 (1·01–14·02)

Table 4: **Associations between HAART programme characteristics in low-income countries and mortality**

Discussion

Mortality rates of HIV-infected patients from low-income settings in Africa, South America, and Asia fell substantially within the first few months of HAART, and approached those seen in Western Europe and North America after 4–6 months. Patients in low-income settings started treatment with considerably more advanced immunodeficiency than those from industrialised countries, but virological and immunological response to HAART were similar in both settings, a finding that tallies with results from a recent collaborative analysis of treatment sites in the Asia and Pacific region,[26,27] a meta-analysis of the literature,[28] and reports from single centres.[29–31]

This systematic comparison of outcomes of HAART between low-income and high-income countries was done in treatment-naïve patients only, and results are therefore not confounded by previous antiretroviral therapy. Patients were enrolled in many different settings, which should reflect the experience with HAART in these regions. A substantial proportion of patients from low-income settings had to be excluded, and the data from low-income settings may thus be less generalisable than those from Europe and North America. Our study was restricted to adults, and results might not be applicable to infants and children. Information on AIDS events before starting treatment was missing for some patients in low-income settings. The statistical methods that we used to deal with this make use of the fact that previous AIDS events are strongly associated with measured factors at initiation, in particular the CD4 cell count, while allowing appropriately for the additional uncertainty due to the missing data.[11,12]

Loss to follow-up is an important issue in treatment programmes in low-income settings. Ascertainment of deaths was clearly incomplete in ART-LINC clinics where no specific attempts were made to trace patients, confirming the results of a study from Côte d'Ivoire.[32]

These sites were excluded from survival analyses. In treatment programmes that actively followed-up patients, individuals lost to follow-up and those followed-up had similar baseline CD4 cell counts: those lost to follow-up were therefore probably not a selected group of patients with worse prognosis. All patients were started on HAART, which was documented for several months in most patients later lost to follow-up. This means that many will have survived the initial months, which have high mortality rates. Finally, our censoring strategy was conservative: follow-up was censored at the last visit. Clearly, some patients lost to follow-up will have died during the first year. In the worst-case scenario, if those lost to follow-up had the same prognosis as untreated patients, their baseline CD4 cell count (115 cells per μL) would mean that 25–50% died within 1 year.[33] This would increase mortality from 6·4% to as high as 15%. A study[34] of 910 adult treatment-naïve patients from Port-au-Prince, Haiti, reported that 13% died during the first year and 8% were lost to follow-up. This difference could suggest under-ascertainment of deaths in ART-LINC. Alternatively, the higher mortality in Port-au-Prince could be due to the more stringent criteria for initiating antiretroviral therapy (clinical AIDS or a CD4 cell count below 200 cells per μL). In ART-LINC, a substantial proportion of patients were free of AIDS at baseline, with a CD4 cell count above 200 cells per L. Notably, in both the Haitian study and ART-LINC about 80% of deaths occurred during the first 6 months.

The higher mortality in low-income countries during the first months of treatment compared with those in Europe and North America was only partly explained by the lower CD4 cell counts and more advanced clinical stage. Comorbidities that are present in many patients starting HAART in resource-poor settings, including tuberculosis and invasive bacterial and fungal infections, might have increased mortality,[35] considering that access to prophylaxis, diagnostic facilities, and effective treatment for opportunistic infections is often limited. Immune reconstitution disease, an adverse consequence of restoration of pathogen-specific immune responses might also be a problem, particularly for tuberculosis.[35] Advanced immunodeficiency is associated with subclinical and disseminated infections, with high mycobacterial antigen load, and rapid improvement of immune function during HAART.[36] Inflammatory reactions occur in about one-third of co-infected patients receiving both HAART and tuberculosis treatment,[36,37] and might have contributed to the higher mortality we noted for sites with dedicated tuberculosis clinics.

However, even in the first months of HAART, mortality was lower than previously noted in untreated patients, suggesting an early beneficial effect of HAART. For example, compared with a mortality rate of 147 per 1000 person-years in the first month after treatment initiation in ART-LINC, mortality was 264 per 1000 person-years in the Cape Town AIDS Cohort[38] of 974 patients not treated with HAART, 353 per 1000 person-years in 746 untreated patients from the Gambia,[39] and 231 per 1000 person-years in a prospective study of 201 untreated Ugandan patients.[40]

Mortality was increased in programmes that charged fees. The World Bank, the International Monetary Fund, and other agencies have been criticised for promoting the privatisation of health services and private financing of health services through user fees.[41,42] Whitehead and colleagues[43] have argued that market-oriented policies can result in untreated morbidity, reduced and more unequal access to care, further impoverishment of those who are already poor, and can promote the inappropriate use of drugs. For example, treatment might have been stopped when money ran out: payments for antiretrovirals during the initial phase of therapy do not mean that households have the ability to pay for extended periods of time. In these settings, treatment might also be more likely to be interrupted and then resumed upon clinical deterioration. Our results extend those from a systematic review and meta-analysis,[28] which recorded that provision of HAART free of charge to the patient was associated with an increased probability of achieving and maintaining suppression of viral replication. Although we acknowledge that other aspects of the delivery of care could have confounded associations, there is concern that the "inverse equity hypothesis", which stipulates that health inequities will get worse as effective new public health interventions initially reach those of higher socioeconomic status and only later the poor, could be borne out in the case of HAART in some resource-poor settings.[44,45]

In many of the countries included in our study, access to potent antiretrovirals continues to be limited. For example, the WHO estimates that as of June, 2005, the percentage of people in urgent need of antiretroviral therapy who received HAART was 4–8% in Nigeria, 4–9% in India, 10–17%% in Côte d'Ivoire, 10–14% in South Africa, 11–14% in Malawi, 12–17% in Kenya, 11–19% in Cameroon, and 35–43% in Uganda.[5] Thailand, Botswana, and Brazil are providing treatment to half or more of people living with HIV/AIDS that need it, consistent with the WHO "3 by 5" target.[5] Clearly, the global health emergency that was declared by the United Nations General Assembly in 2001 continues.

Antiretroviral therapy is feasible and effective in low-income settings, but, compared with industrialised countries, mortality is high in the first months. Eligibility for antiretroviral treatment and the need for treatment of tuberculosis should be determined earlier, and HAART should be started before serious co-morbidities develop. The scaling-up of HAART should therefore be accompanied by an expansion of voluntary counselling and testing services, and by efforts to reduce the stigma and adverse social effects associated with a positive HIV test, which might encourage more people at risk of HIV to seek testing.

Contributors

F Dabis, M Egger, and M Schechter conceived the ART-LINC Collaboration and wrote the first draft of the study protocol. All collaborators contributed to the final version of the protocol. M Egger conceived and coordinated the current analyses. M Brinkhof, M May, and J Sterne did statistical analyses. M Egger and P Braitstein wrote the first draft of the paper; all authors contributed to the final text. All investigators assisted in implementation, fieldwork, or data collection at study sites.

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Conflict of interest statement

P Miotti is a staff member of the National Insititute of Health (NIH). The NIH cofunds ART-LINC with the French AIDS research agency ANRS. M May's salary is jointly funded by the Medical Research Council (which funds the ART Cohort Collaboration and other HIV projects) and the British Heart Foundation (CHD projects); she has received travel grants for GlaxoSmithKline for travel to ART-CC meetings, but declares no conflict of interest with respect to this paper. J Sterne has received travel grants from GlaxoSmithKline. The other coauthors declare that they have no conflict of interest.

Acknowledgments

The ART-LINC Collaboration is funded by the US National Institutes of Health (Office of AIDS Research) and the French Agence Nationale de Recherches sur le Sida (ANRS). The Art Cohort Collaboration is funded by the UK Medical Research Council. We thank Michel Kazatchkine and Brigitte Bazin for their encouragement and support; all the patients and collaborating centre staff who made this project possible; Martin Schneider, Gorana Capkun, and Malcom Sturdy for their help and advice; Besigin Tonwe-Gold (Abidjan) and Jessica Oyugi (Kampala) for their assistance in the field; Manuel Battegay, Geneviève Chêne, Dominique Costagliola, Hansjakob Furrer, Bernhard Hirschel, Nicola Low, and Amalio Telenti for comments on an earlier draft of this report.

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